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High prevalence of bronchiectasis in patients with cartilage-hair hypoplasia

To the Editor:

Cartilage-hair hypoplasia (CHH, MIM #250250) is a metaphyseal chondrodysplasia with variable immunodeficiency and increased risk of malignancy. We previously showed that in patients with CHH with chronic respiratory symptoms, the prevalence of bronchiectasis (BE) is 52%.[1] The prevalence of BE and the contributing risk factors in the overall CHH population remain unknown. High-resolution computed tomography (HRCT) is the criterion standard investigation for assessing BE; however, radiation exposure is a concern. Pulmonary changes in patients with CHH have not been examined systematically and the applicability of lung magnetic resonance imaging (MRI) in assessing their lung pathology is unclear.

We investigated the prevalence of BE in a random cohort of 34 Finnish patients with genetically confirmed CHH (6 men, 28 women; median age, 39 years, range, 13-68 years). All patients or caregivers gave their written informed consent. The Institutional Research Ethics Committee approved the study. We collected clinical data, obtained blood tests, and performed lung HRCT (34 of 34) and MRI (16 of 34) (for detailed imaging protocols, see Appendix E1 in this article's Online Repository at www.jacionline.org). We analyzed the clinical and immunologic correlates with BE with the Fisher exact test, the Mann-Whitney test, and multiple logistic regression analysis. Performance of MRI compared with HRCT was determined by the Spearman rank correlation coefficient (rho).

Table I presents the patients' clinical and laboratory characteristics. HRCT showed BE in 10 of 34 patients (29%), aged 29 to 68 years. BE was unilateral (n = 2) or bilateral (n = 8) and was located most commonly in the lower lobes and right middle lobe, but was also found in all other lobes (Fig 1). Additional findings on HRCT were acute inflammation (n = 3), fibrosis-like changes (n = 6), and nonspecific subpleural nodules of less than 0.5 cm in size (n = 8). MRI showed lung abnormalities in 8 of 16 patients and had a good correlation with HRCT (overall ρ, 0.820; $P < .001$) (see Table E1 in this article's Online Repository at www.jacionline.org).

Patients with BE had significantly higher serum IgG and white blood cells, total lymphocyte, and CD16/56$^+$ cell counts (Table I). However, these parameters correlated significantly with age (see Fig E1 in this article's Online Repository at www.jacionline.org). Patients with BE tended to have more sinus infections, pneumonia, and chronic cough (defined as ongoing daily cough lasting ≥1 year). BE was diagnosed in 4 of 6 patients with a history of smoking, but when controlled for age, this association became insignificant. In the multiple logistic regression analysis, only higher CD16/56$^+$ cell counts remained associated with the presence of BE ($P = .026$; B coefficient, 8.8). Humoral immune defect (defined as IgA deficiency or low IgM levels or low levels of at least 2 IgG subclasses or ongoing intravenous immunoglobulin substitution) was insignificantly more common in patients with BE (5 of 10 vs 11 of 24). Preexisting antibodies to tetanus toxoid were below the protective level in 2 of 27 patients, both aged 68 years, one with BE and another without. Serologic responses to polysaccharide pneumococcal vaccine (measured in 5 patients) were abnormal in subjects with and without BE. Retrospective data on lymphocyte mitogen stimulation showed decreased responses in 6 of 8 patients, all without BE. Noteworthily, 2 patients with BE had normal laboratory parameters, except for low CD27$^+$IgD$^+$ B cells.

BE is a known complication of combined variable immunodeficiency and detected in more than 20% of patients,[7] corresponding to the prevalence of 29% in our study cohort. However, our findings suggest that BE often develops also in CHH patients with inapparent immunodeficiency, implicating the presence of other contributing factors. Hyaline cartilage, in contrast to growth plate cartilage, is not affected in CHH and thus tracheal and bronchial defects are unlikely to play a role. Although the underlying cause of BE cannot be detected on the basis of lobar involvement, the distribution of BE in our cohort was similar to the pattern in patients with bronchiolitis obliterans.[8] This echoes our finding of fibrosis-like changes in 18% of patients with CHH and requires further studies. Most of our patients reported absent or mild respiratory symptoms and had never been evaluated by lung HRCT. However, half of those with BE reported chronic cough, emphasizing the need for regular follow-up even in mildly symptomatic individuals. Also, in individuals with short stature and BE of unknown etiology, the diagnosis of CHH should be considered.

In patients with immunodeficiency, lung disease such as BE or parenchymal changes contribute to poorer prognosis.[6] Out of 8 previously reported patients with BE, 1 died from pneumonia at 58 years; others had significant respiratory symptoms and 6 suffered from pneumonia.[1] BE was progressive in all those with longitudinal follow-up extending to adulthood.[1] Another report described a young adult with CHH, frequent infectious exacerbations and rapid progression of BE, leading to fatal septicemic pneumonia within 2 years.[9]

We previously reported higher IgG levels in infection-prone patients with CHH.[2] Here, we find the same trend, as well as higher white blood cells, total lymphocyte, and CD16/56$^+$ cell counts in CHH patients with BE. These findings may be explained by exacerbated inflammatory responses in the respiratory tract, smoking, chronic smoldering infections, impaired specific antibody production, or BE-induced systemic immune response.[10]

Patients in our cohort more often had low CD19$^+$ (67% [22 of 33]) than low CD3$^+$ (33% [11 of 33]) cell counts. Total IgG concentrations were normal in all, including levels in patients before initiation of IVIG therapy. However, almost half the patients (47%) had humoral immune defects and 4 of 5 tested patients showed specific antibody deficiency, suggesting that immunoglobulin substitution may be beneficial despite normal IgG levels. We excluded 3 patients receiving IVIG at the time of the study from IgG and subclass analysis. However, when we included IgG levels available for 2 of these patients before initiation of IVIG therapy, the difference between median IgG levels in patients with and without BE became even more significant ($P = .009$).

TABLE I. Comparison of clinical and laboratory characteristics of patients with and without BE

Characteristics	Normal values for adults*	Patients with BE	Patients without BE	*P* value
Median age (y) (range)		59.5 (29-68)	36.5 (13-68)	**.023**†
Sex		F 70% (7 of 10) M 30% (3 of 10)	F 88% (21 of 24) M 12% (3 of 24)	.328
History of chronic cough		50% (5 of 10)	17% (4 of 24)	.085
History of sinusitis		90% (9 of 10)	63% (15 of 24)	.215
History of otitis media		70% (7 of 10)	75% (18 of 24)	1
History of pneumonia‡		30% (3 of 10)	21% (5 of 24)	.666
History of physician-diagnosed asthma		30% (3 of 10)	29% (7 of 24)	1
History of allergic rhinitis		60% (6 of 10)	38% (9 of 24)	.276
History of smoking		40% (4 of 10)	8% (2 of 24)	**.048**
Previous or ongoing IVIG substitution		0% (0 of 10)	17% (4 of 24)	.296
IgG (g/L)	6.8-15.0	13.0 (10.1-15.7)	10.6 (6.2-15.9)	**.013**
IgG_2 (g/L)	1.50-6.40	2.03 (0.27-4.01)	2.00 (0.55-4.52)	.755
IgG_3 (g/L)	0.20-1.10	0.43 (0.17-1.17)	0.45 (0.12-1.20)	.724
IgG_4 (g/L)	0.08-1.40	0.09 (0.00-0.82)	0.08 (0.00-0.47)	.724
IgA (g/L)	M 0.88-4.84 F 0.52-4.02	2.82 (1.24-4.95)	1.83 (0.00-7.49)	.086
IgM (g/L)	M 0.36-2.59 F 0.47-2.84	0.89 (0.28-2.47)	0.99 (0.20-3.06)	.512
IgE (kU/L)	0-100	34 (10-98)	13 (2-254)	.205
WBC ($\times 10^9$ cells/L)	3.4-8.2	6.8 (4.7-12.0)	4.8 (1.2-11.1)	**.034**
Neutrophil count ($\times 10^9$ cells/L)	1.5-6.7	4.26 (2.22-8.40)	3.31 (0.28-7.88)	.137
Total lymphocyte count ($\times 10^9$ cells/L)	1.3-3.6	1.76 (1.16-3.25)	1.21 (0.26-2.22)	**.008**
$CD3^+$ cell count ($\times 10^9$ cells/L)	0.85-2.28	1.24 (0.57-3.01)	0.90 (0.16-1.91)	.051
$CD4^+$ cell count ($\times 10^9$ cells/L)	0.458-1.406	0.711 (0.353-1.287)	0.524 (0.118-1.312)	.123
$CD8^+$ cell count ($\times 10^9$ cells/L)	0.24-0.98	0.52 (0.15-1.72)	0.30 (0.04-0.76)	.068
$CD3/CD4/CD45RA/CD31^+$ cell count ($\times 10^9$ cells/L)	0.05-2.4	0.011 (0.003-0.171)	0.030 (0.000-0.247)	.269
$CD16/56^+$ cell count ($\times 10^9$ cells/L)	0.08-0.57	0.25 (0.11-0.55)	0.14 (0.07-0.36)	**.008**
$CD19^+$ cell count ($\times 10^9$ cells/L)	0.12-0.43	0.11 (0.04-0.22)	0.11 (0.00-0.28)	.524
$CD27^+$ IgD^+ B-cell count (cells/μL)	9-88	5,9 (2.9-13.3)	6.5 (0.0-20.9)	.603
$CD27^+$ IgD^- B-cell count (cells/μL)	13-122	12.8 (3.9-59.6)	10.6 (0.0-63.8)	.269
Antibodies to tetanus toxoid (IU/mL)	>0.1	2.85 (0.07-4.60)	2.35 (0.05-8.90)	.621
Good response to immunization with PPV (no. of serotypes)§	7	4 (3-5)	6 (1-7)	.773

Values for laboratory parameters are presented as median (range). *P* values less than .05 were considered significant and are in boldface.
BE, Bronchiectasis; *F*, female; *IVIG*, intravenous immunoglobulin; *M*, male; *PPV*, polysaccharide pneumococcal vaccine (Pneumovax); *WBC*, white blood cell.
*Local laboratory or previously published reference values[2-6] were applied for the tested parameters.
†Spearman correlation coefficient (rho) 0.392 ($P = .022$).
‡One patient with BE and 3 patients without BE had a history of recurrent pneumonia.
§*Good response* was defined as a 4-fold rise in serotype-specific antibodies measured with fluoroimmunoassay and a postimmunization antibody level of ≥0.35 μg/mL.

Asthma and allergic rhinitis were significantly more prevalent in our cohort than in the general population of Finnish adults (24% vs 6% and 44% vs 15% to 25%, respectively).[11,12] These conditions may have been misdiagnosed as the cause of respiratory symptoms in some of the patients, or individuals with CHH suffer from immune dysregulation. Serum total IgE level was normal in 31 patients and increased in 1 subject (Table I) who had no allergic symptoms, but reported repeated sinusitis in adulthood. Asthma diagnostics in CHH is complicated by difficulties in interpreting spirometry due to short stature and absence of disease-specific reference values. Asthma diagnosis should not replace lung imaging in CHH patients with chronic respiratory symptoms.

Lung HRCT remains the criterion standard for diagnosing BE, but we found a good correlation between HRCT and MRI scores when assessing BE in patients with CHH. Lung MRI may potentially thus replace HRCT in follow-up, sparing these malignancy-prone patients from repeated radiation exposure.

We recognize some limitations in our study. We recruited patients regardless of their clinical presentation and this may have led to selection bias. However, most participants had no current respiratory complaints. Patients deceased from infections or aggressive lymphoma may constitute a more severely affected group that was absent from our cohort. However, 2 of our patients had survived lymphoma, and 4 were on immunoglobulin therapy, representing more severely immunocompromised subjects. We did not systematically screen for other potential causes of BE, but our patients with BE (youngest 29 years) lacked typical symptoms of cystic fibrosis or primary ciliary dyskinesia, both of which have low prevalence in Finland. Lymphocyte proliferative responses to mitogens were not systematically evaluated because we[13] and others[14] have previously shown that responses are abnormal in most of the patients and correlate poorly with clinical parameters in CHH. Of the patients with BE, 6 of 10 were older than 58 years, and the prevalence of BE in this age group in healthy individuals is around 15%.[15] However, the prevalence in this age group was significantly higher (55%, 6 of 11) in our cohort. We diagnosed BE in a patient as young as 29 years, underscoring the necessity of early BE screening.

Because BE can lead to recurrent lung infections and even death in patients with CHH, lung pathology should be actively

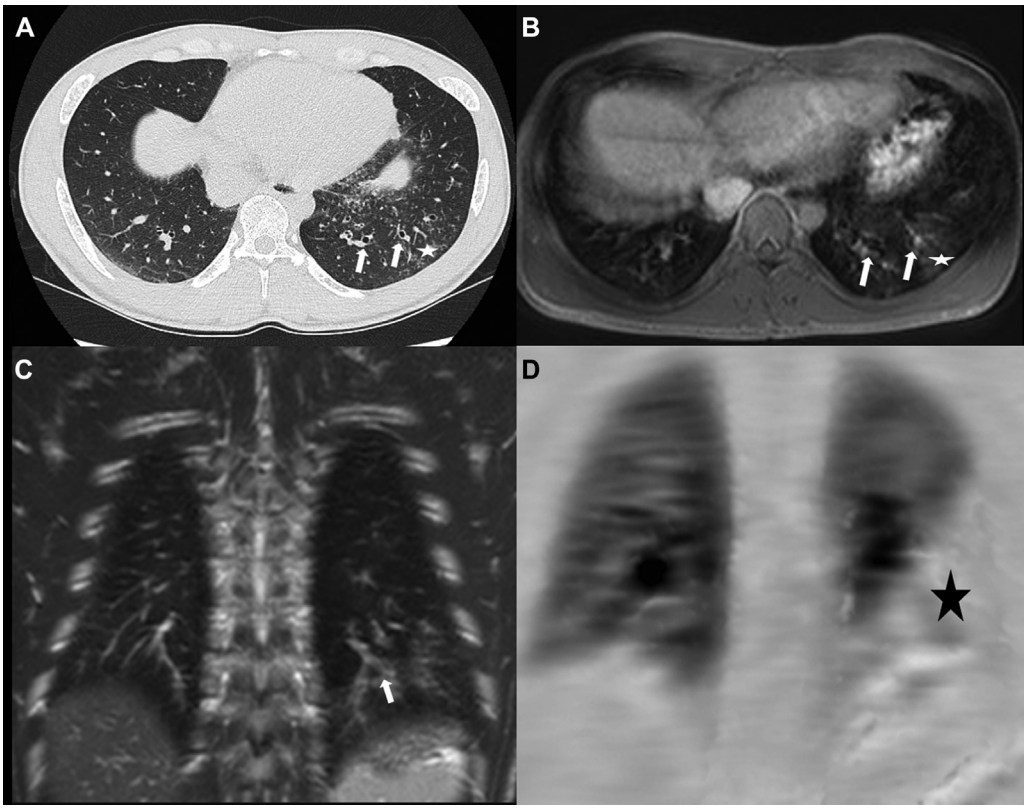

FIG 1. Lung abnormalities on MRI and HRCT images of a 35-year-old male patient with CHH. A male patient aged 35 years with bronchiectasis *(white arrows)* and mucous plugging *(white asterisks)* in the left lower lobe on axial HRCT slice **(A)** and MRI (**B**, Axial gadolinium-enhanced T1-weighted gradient-echo sequence; **C,** coronal breath-hold Single Shot Turbo Spin Echo). With gadolinium-enhanced dynamic perfusion T1-weighted sequence **(D)**, hypoperfusion of the left lower lobe *(black asterisk)* was observed.

searched for and treated. Even in asymptomatic patients, the diagnosis of BE influences ongoing management and treatment of possible future respiratory infections. Given the applicability and safety of lung MRI, we recommend scheduled lung imaging in all adults with CHH. Prospective studies are needed to determine the rate of BE progression and mortality, and to elucidate the pathogenetic mechanisms leading to BE development in CHH.

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Corrections

With regard to the article in the October 2016 issue entitled "Rapid molecular diagnostics of severe primary immunodeficiency determined by using targeted next-generation sequencing" (J Allergy Clin Immunol 2016;138:1142-51.e2), the authors wish to note 2 incorrect terms. In Table II (page 1145), one of the *JAK3* pathogenic variants for the S2 sample should be corrected as "c.2297_2298delAGinsC (p.Q766Pfs*79)," rather than "c.2297_2298delAGinsC (p.R767Efs*10)." Additionally, in the first paragraph of the last results section "Leaky SCID and combined variable Immunodeficiencies" (page 1146) and Table IV (page 1149), the homozygous *RAG1* variant of Patient 15 (P15) should be corrected as "c.1541T>G (p.L514R)," rather than "c.1514T>G (p.L514R). The authors regret these errors.

With regard to the article in the October 2016 issue entitled "Pharmacogenomics and adverse drug reactions: Primetime and not ready for primetime tests" (J Allergy Clin Immunol 2016;138:943-55), it has been brought to the Editors' attention that an incorrect gene was used in the upper paragraphs in the second column on page 951. The term HLA-B*1502 is used instead of HLA-B*5801. The authors regret the error.